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Commentary

Generic substitution

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Generic substitution is the term applied to the substitution of a prescribed branded drug by a different form of the same active substance. The generic is usually unbranded; it is often a parallel imported product, which is regarded as 'essentially similar' by the EU Commission. Generic substitution becomes possible when the patent life of the active substance has expired.

In the UK, generic substitution was raised as a means of reducing the NHS medicines bill in the Greenfield Report of 1983 [1]. The proposal was not implemented, but an initiative to encourage generic prescribing resulted in a change in doctors' prescribing habits towards the greater use of generics. Within a decade, the overall shape of the NHS market had changed dramatically, so that by 1993 generic products accounted for 11% of the NHS expenditure on drugs and 41% of the volume. Prescriptions for branded products within their patent life accounted for 26% by value but only 7% by volume. The bulk of the NHS prescription market, 63% by value and 52% by volume, comprised active substances that were out of patent but still prescribed by brand name. Clearly, there was room for further savings by encouraging greater prescribing of generics, and it was considered likely that government negotiations in 2009 on the long-established Pharmaceutical Price Regulation Scheme (PPRS) [2] would result in mandatory generic substitution, but this was not adopted.

The pricing of generic products in the UK is set by the Drug Tariff Scheme, which is a reference price scheme in which the average price for each generic formulation is determined by the average price of the four/five largest manufacturers of each generic formulation. The community pharmacist who dispenses the generic is reimbursed at the tariff price. The pharmacist therefore does not purchase generic preparations from manufacturers whose price is above the tariff price. This effectively forces a downward price spiral.

Outside the UK, generic substitution was implemented by a number of reimbursement authorities, insurance-based schemes in the USA and national healthcare services, such as those in Sweden (introduced October 2002) and Finland (introduced April 2003). Both Sweden and Finland claimed considerable savings, of the order of 5% of national expenditure on medicines.

Marketing authorization of each formulation of a generic medicine is dependent on demonstration of bioequivalence to a reference, often the branded product. Bioavailability of the active substance must be equivalent to the reference within narrow margins. These stringent requirements mean that there should be very little concern among prescribers and the general public about the quality and comparability of generics to the branded products.

Filling prescriptions with parallel imported products from different EU countries, where 'essential similarity' rather than bioequivalence is the criterion for marketing approval, does not offer comparable assurance though, as far as we know, there is little evidence of a clinically significant problem.

Of much greater concern is the problem of counterfeit products. In an interview with the *Daily Telegraph* (April 2008), Mick Deats, a former Detective Chief Superintendent of the MHRA intelligence and enforcement unit, stated that in Britain, from August 2004 to the end of 2007, there had been nine product recalls of counterfeit medicines where there was clear evidence that fakes had reached pharmacies and patients. Counterfeit medicines represent a more serious threat to patient safety than the theoretical problems that may arise from generic substitution.

Perhaps the most important factor impacting the safety and effectiveness of generic products is their appearance. Currently, the pharmacist may dispense generics from different manufacturers that bear no physical resemblance to the branded product or to one another. Inevitably, this confuses patients on long-term treatment with multiple medicines. In our view, it should be a regulatory requirement for generic products to be of similar appearance to that of the branded product, while being clearly distinguishable from it. For patients to know that a particular drug will always be of the same size, shape and colour, from one prescription to the next and regardless of which pharmacist has dispensed it, would represent a simple but major advance in therapeutics. When the branded product is no longer available or contributes little to the volume of sales, different generic formulations of a particular dose of a drug should still be required to resemble each other.

The implications of therapeutic substitution, the replacement of one prescribed drug by an alternative drug with assumed equivalent therapeutic effect, depend, to some extent, on whether the replacement is of the same or a different class. A moment's consideration of the different properties of the large variety of drugs used for a single indication, e.g. heart failure or diabetes, makes it abundantly clear that the choice of the most appropriate drug/s

for an individual patient should always be a matter for the prescribing doctor. In contrast, the drive to use less expensive medicines will often result in the doctor prescribing a generic medicine rather than a patented one of the same class. This may be perfectly satisfactory, though it should be recognized that the properties of drugs of the same class may differ considerably. A classic example from the 1980s is the difference in propensity to metabolic drug interactions between ranitidine and cimetidine. In our view, therapeutic substitution is fraught with hazards and, rightly, has never been seriously considered by Government as a cost-containment measure in the UK.

The dramatic growth of biological medicinal products in recent years has focused attention on 'biosimilars'. The complexity of bioengineered constructs makes the question of whether a product is comparable in quality to a branded product far more demanding than for small molecules. Quantitative bioequivalence is only one aspect of 'biosimilarity', and pharmacokinetic data alone are unlikely to be adequate. To date, there are very few approved biosimilars, and it remains to be seen exactly how much clinical trial data will be required to establish comparability. A European Medicines Agency guideline lays down the general requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy [3]. Very recently, a draft guideline has been issued by the European Medicines Agency providing greater detail on demonstration of biosimilarity of two monoclonal antibody-containing medicinal products [4]. There is no doubt that for many such products, demonstration of similarity will require use of pharmacodynamic end-points and measures of clinical efficacy and safety in patients. Concerns about known uncommon but serious adverse reactions imply that more than routine pharmacovigilance will be required post-authorization. Consideration will also need to be given to unwanted immunogenicity [5].

The cost of medicines to national and private healthcare services is, of course, a major consideration in all countries. However, any discussion of the importance of generic substitution must also take into account the needs of the pharmaceutical industry, because the discovery and development of new medicines is entirely dependent on companies' ability to see a return on their investment. With ever increasing regulatory requirements, the cost and duration of drug development have increased inexorably over the past half century, and there has been a corresponding erosion of patent life remaining after marketing authorization. The response of companies has been to market their new products aggressively, aiming to achieve peak sales in the shortest possible time. This is a highly undesirable situation with respect to patient safety, as experience with a new product at the time it receives marketing authorization is necessarily limited to the clinical trial population. If the erosion of patent life before generic substitution continues, it will become less attractive for companies to invest in innovative research and development. The *quid pro quo* needs to be considered carefully, but additional years of marketing exclusivity in return for restricting patient exposure while post-licensing safety studies are conducted is one possible solution.

In summary, generic substitution of branded products has played an important role in limiting the cost of medicines in many countries, and strict regulatory requirements have ensured that marketed generics are bioequivalent to branded products. Additional regulatory requirements for similarity of appearance could prevent much confusion of patients when taking their medicines. Therapeutic substitution is hazardous and should not be entertained as a cost-saving measure. Demonstration of comparability between biological products presents a new challenge. Consideration should be given to delaying entry of generic products to the market in return for restricting access to the market of newly licensed branded products for a period while key safety studies are conducted.

Competing Interests

There are no competing interests to declare.

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